If applicant desires priority under 35 U.S.C. § 120 based upon a parent application, specific reference to the parent application must be made in the instant application. It is noted that this appears as the first sentence of the specification following the title. Status of the parent application (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "Patent No." should follow the filing date of the parent application. If a parent application has become abandoned, the expression "abandoned" should follow the filing date of the parent application.

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The title lacks specificity to retinoblastoma gene methods and thus is overly broad.

Drawings in colors other than black and white do not come within the purview of 37 CFR 1.84. Unless the drawing requirements of 37 CFR 1.84 are waived, the draftsman will not approve color drawings in a utility or design patent application. Thus, Figures 13A-13I, 14, 15A, 15B, 16A, 16B, 17A, 17B, 18A, 18B, 19A, 19B, 20, and 21 are improper and applicants must either cancel the drawings or provide substitute black and white drawings.

Neither the examiner nor the draftsman have the authority to waive or suspend drawing requirements to permit color drawings in utility and design applications. Applicants may file a petition under 37 CFR 1.183 with fee requesting acceptance of the color drawings and a waiver of the requirements of 37 CFR 1.84. The petition and application file must be sent to the Deputy Assistant Commissioner for Patents for decision. Only if the petition is granted will the draftsman be authorized to approve

the color drawings as to form.

Where color drawings have been transferred from a prior application to a newly submitted application, applicants must renew the petition under 37 CFR 1.183 even though a similar petition was filed in the prior application. Until the renewed petition is granted, the examiner must object to the color drawings as improper. See MPEP 608.02.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

On pages 137-147 of the specification there is described the detection of chromosome 3/17 aberrations. This is the only disclosure in the specification directed at these chromosomes. The cell lines studied are listed on page 141, first paragraph. None of those cell lines nor the accompanying discussion involve the retinoblastoma gene as claimed in claim 1, for example. Thus there is a lack of instant enablement that a chromosome 3/17 rearrangement is associated with the retinoblastoma gene as claimed in claim 1 etc.

Claims 8-13 are also rejected because they are directed to a cancer detection without guidance as to the the association practice cited in line 2 of claim 8. The data in Table 4 on page 135 is insufficient to show said association due to a lack of controls as well as data directed at diagnostic use practice as to what specific determination would be correlative between various samples and cancer diagnosis. Since only tumor samples are analyzed in said Table, there is no test practice set forth that illustrates what result is normal or non-cancerous. Without such control values to compare to as well as cancer cell values so as to define distinguishing result for cancer, the practitioner is left with no prediction regarding cancer vs. non-cancer. This unpredictability of result is indicative of undue experimentation thus supporting this rejection. See the MPEP § 608.01(p), section on 35 U.S.C. 101.

Claims 1-20 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the above objection to the specification.

Claims 1-20 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to retinoblastoma rearrangement detection wherein there is used the specific primers showing chromosomal rearrangements involving chromosomes 13 and 21 as given in Example IX starting on page 130 of the specification. There is no guidance or enablement of involvement of other chromosomes or primers. There is especially no guidance as to what is meant as to the location of "the

vicinity" given in claim 1, line 3. Additionally, the reference cited by applicants as Bowcock et al. has been enclosed in the previous office action and summarizes in the abstract that the linkage between the chromosome 13 RB gene and cancer is not clear and may be secondary or present in some tumors only be chance. Thus even the instantly discussed rearrangement is in question as to its enablement. See M.P.E.P. §§ 706.03(n) and 706.03(z).

Claims 1-20 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-20 are vague and indefinite in that they are supposedly method claims but do not recite even a single positive method step.

Claims 1-20 are vague and indefinite in that they cite a nucleic acid sequence (e.g. claim 1, line 2) as if it was a composition. A "sequence" of a nucleic acid is a characteristic of said nucleic acid and not a composition in itself. Thus citing a sequence as a composition is confusing and unclear as to what is meant. Clarification is requested.

Claims 15-20 are rejected under 35 U.S.C. § 112, fourth paragraph, as being of improper dependent form for failing to further limit the subject matter of a previous claim.

Claims 15-20 broaden rather than further limit the scope of claim 1 from which each ultimately depends. Claim 1 is limited to probes only for chromosomes 3 and/or 17 and do not cover a

scope including other chromosomes. Therefore, the added chromosomes 13 and 21 in claim 15 are not further limiting from claim 1.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 1-20 are rejected under 35 U.S.C. § 103 as being unpatentable over Weissman et al.

The instant invention is directed to the use of high complexity probes for hybridization labeling of chromosomes to detect rearrangements that may be associated with various disease

states.

Weissman et al. disclose in columns 5-6, bridging paragraph, that the invention therein described detects chromosomal arrangements such as the spacing between genes including linkage that may be related to a disease. Probed regions are disclosed as 50 kb to 2000 kb in column 9, lines 14-32, which clearly qualifies as high complexity probes as instantly claimed. The coverage of the probed region is accomplished as depicted in Figure 5 (discussed in column 18, lines 32-62) and discussed as to probes prepared in the bridging paragraph between columns 18 and 19. Weissman et al. lacks the specific retinoblastoma rearrangement disclosure but is motivated to study such rearrangements as summarized in column 2, line 13, through column 4, line 5.

Thus, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to practice high complexity probes and their use in hybridization assay as instantly claimed because Weissman et al. disclose the method and the motivation to apply this to diseases suspected of being caused by genetic rearrangements such as retinoblastoma gene rearrangements that result in cancer.

The references cited herein have been made of record in the parent application 08/312,914 and are hereby also made of record in the instant application.

The disclosure is objected to because of the following informalities:

On page 18, the citation to Waldman et al. is incomplete.

On pages 131, 140, 144 and 145; lines 2, 11, 25, and 11; respectively; the citations are incomplete.

Appropriate correction is required.

No claim is allowed.

This is a file-wrapper-continuation of applicant's earlier application S.N. 08/312,914. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds or art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See M.P.E.P. § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

This application is subject to the provisions of Public Law 103-465, effective June 8, 1995. Accordingly, since this application has been pending for at least two years as of June 8, 1995, taking into account any reference to an earlier filed application under 35 U.S.C. 120, 121 or 365(c), applicant, under 37 CFR 1.129(a), is entitled to have a first submission entered

and considered on the merits if, prior to abandonment, the submission and the fee set forth in 37 CFR 1.17(r) are filed prior to the filing of an appeal brief under 37 CFR 1.192. Upon the timely filing of a first submission and the appropriate fee of $ 365.00 for a small entity under 37 CFR 1.17(r), the finality of the previous Office action will be withdrawn. In view of 35 U.S.C. 132, no amendment considered as a result of payment of the fee set forth in 37 CFR 1.17(r) may introduce new matter into the disclosure of the application.

If applicant has filed multiple proposed amendments which, when entered, would conflict with one another, specific instructions for entry or non-entry of each such amendment should be provided upon payment of any fee under 37 CFR 1.17(r).

Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)). The CM1 Fax Center number is either (703) 305-7401 or (703) 305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ardin Marschel, Ph.D., whose telephone number is (703) 308-3894. The examiner can normally be reached on Monday-Friday from 8 A.M. to 4 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the Chemical Matrix receptionist whose telephone number is (703) 308-0196.

September 3, 1996

Ardin H. Marschel

ARDIN H. MARSCHEL
PATENT EXAMINER
GROUP 1800

If applicant desires priority under 35 U.S.C. § 120 based upon a parent application, specific reference to the parent application must be made in the instant application. It is noted that this appears as the first sentence of the specification following the title. Status of the parent application (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "Patent No." should follow the filing date of the parent application. If a parent application has become abandoned, the expression "abandoned" should follow the filing date of the parent application.

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The title lacks specificity to retinoblastoma gene methods and thus is overly broad.

Enclosed is an executed PTO Form 1449 with several citations thereon lined through. They are lined through because review of parent serial number 07/627,707 as noted by applicants revealed that these references were not cited therein nor have applicants supplied copies for consideration.

Drawings in colors other than black and white do not come within the purview of 37 CFR 1.84. Unless the drawing requirements of 37 CFR 1.84 are waived, the draftsman will not approve color drawings in a utility or design patent application. Thus, Figures 13A-13I, 14, 15A, 15B, 16A, 16B, 17A, 17B, 18A, 18B, 19A, 19B, 20, and 21 are improper and applicants must either cancel the drawings or provide substitute black and white drawings.

Neither the examiner nor the draftsman have the authority to waive or suspend drawing requirements to permit color drawings in utility and design applications. Applicants may file a petition

under 37 CFR 1.183 with fee requesting acceptance of the color drawings and a waiver of the requirements of 37 CFR 1.84. The petition and application file must be sent to the Deputy Assistant Commissioner for Patents for decision. Only if the petition is granted will the draftsman be authorized to approve the color drawings as to form.

Where color drawings have been transferred from a prior application to a newly submitted application, applicants must renew the petition under 37 CFR 1.183 even though a similar petition was filed in the prior application. Until the renewed petition is granted, the examiner must object to the color drawings as improper. See MPEP 608.02.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

On pages 137-147 of the specification there is described the detection of chromosome 3/17 aberrations. This is the only disclosure in the specification directed at these chromosomes. The cell lines studied are listed on page 141, first paragraph.

None of those cell lines nor the accompanying discussion involve the retinoblastoma gene as claimed in claim 1, for example. Thus there is a complete lack of instant enablement that a chromosome 3/17 rearrangement is associated with the retinoblastoma gene as claimed in claim 1 etc.

Claims 8-13 are also rejected because they are directed to a cancer detection without guidance as to the the association practice cited in line 2 of claim 8. The data in Table 4 on page 135 is insufficient to show said association due to a lack of controls as well as data directed at diagnostic use practice as to what specific determination would be correlative between various samples and cancer diagnosis. Since only tumor samples are analyzed in said Table, there is no test practice set forth that illustrates what result is normal or non-cancerous. Without such control values to compare to as well as cancer cell values so as to define distinguishing result for cancer, the practitioner is left with no prediction regarding cancer vs. non-cancer. This unpredictability of result is indicative of undue experimentation thus supporting this rejection. See the MPEP § 608.01(p), section on 35 U.S.C. 101.

Claims 1-20 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 1-20 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to retinoblastoma rearrangement detection wherein there is used

the specific primers showing chromosomal rearrangements involving chromosomes 13 and 21 as given in Example IX starting on page 130 of the specification. There is no guidance or enablement of involvement of other chromosomes or primers. There is especially no guidance as to what is meant as to the location of "the vicinity" given in claim 1, line 3. Additionally, the reference cited by applicants as Bowcock et al. has been enclosed in the previous office action and summarizes in the abstract that the linkage between the chromosome 13 RB gene and cancer is not clear and may be secondary or present in some tumors only be chance. Thus even the instantly discussed rearrangement is in question as to its enablement. See M.P.E.P. §§ 706.03(n) and 706.03(z).

Claims 1-20 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-20 are vague and indefinite in that they are supposedly method claims but do not recite even a single positive method step.

Claims 1-20 are vague and indefinite in that they cite a nucleic acid sequence (e.g. claim 1, line 2) as if it was a composition. A "sequence" of a nucleic acid is a characteristic of said nucleic acid and not a composition in itself. Thus citing a sequence as a composition is confusing and unclear as to what is meant. Clarification is requested.

Claims 15-20 are rejected under 35 U.S.C. § 112, fourth

paragraph, as being of improper dependent form for failing to further limit the subject matter of a previous claim.

Claims 15-20 broaden rather than further limit the scope of claim 1 from which each ultimately depends. Claim 1 is limited to probes only for chromosomes 3 and/or 17 and do not cover a scope including other chromosomes. Therefore, the added chromosomes 13 and 21 in claim 15 are not further limiting from claim 1.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 1-20 are rejected under 35 U.S.C. § 103 as being unpatentable over Weissman et al.

The instant invention is directed to the use of high complexity probes for hybridization labeling of chromosomes to detect rearrangements that may be associated with various disease states.

Weissman et al. disclose in columns 5-6, bridging paragraph, that the invention therein described detects chromosomal arrangements such as the spacing between genes including linkage that may be related to a disease. Probed regions are disclosed as 50 kb to 2000 kb in column 9, lines 14-32, which clearly qualifies as high complexity probes as instantly claimed. The coverage of the probed region is accomplished as depicted in Figure 5 (discussed in column 18, lines 32-62) and discussed as to probes prepared in the bridging paragraph between columns 18 and 19. Weissman et al. lacks the specific retinoblastoma rearrangement disclosure but is motivated to study such rearrangements as summarized in column 2, line 13, through column 4, line 5.

Thus, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to practice high complexity probes and their use in hybridization assay as instantly claimed because Weissman et al. disclose the method and the motivation to apply this to diseases suspected of being caused by genetic rearrangements such as retinoblastoma gene rearrangements that result in cancer.

The references cited herein have been made of record in the parent application 08/137,745 and are hereby also made of record in the instant application. Since copies have been previously sent to applicants, they are not herewith resent.

The disclosure is objected to because of the following informalities:

On page 18, the citation to Waldman et al. is incomplete.

On pages 131, 140, 144 and 145; lines 2, 11, 25, and 11; respectively; the citations are incomplete.

Appropriate correction is required.

No claim is allowed.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

The CM1 Fax Center number is (703) 305-3014 or (703) 308-4227.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ardin Marschel, Ph.D., whose telephone number is (703) 308-3894. The examiner can normally be reached on Monday-Friday from 8 A.M. to 4 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Margaret Parr, can be reached on (703) 308-2454.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

M. Parr 2/21/95

A. MARSCHEL:am
February 17, 1995

MARGARET PARR
SUPERVISORY PATENT EXAMINER
GROUP 1800

If applicant desires priority under 35 U.S.C. § 120 based upon a parent application, specific reference to the parent application must be made in the instant application. It is noted that this appears as the first sentence of the specification following the title. Status of the parent application (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "Patent No." should follow the filing date of the parent application. If a parent application has become abandoned, the expression "abandoned" should follow the filing date of the parent application.

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The title covers methods only whereas the instant claims are also directed to compositions. Also the title is lacking as to the retinoblastoma central aspect of the invention.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

On pages 137-147 of the specification there is described the detection of chromosome 3/17 aberrations. This is the only disclosure in the specification directed at these chromosomes. The cell lines studied are listed on page 141, first paragraph.

None of those cell lines nor the accompanying discussion involve the retinoblastoma gene as claimed in claim 1, for example. Thus there is a complete lack of instant enablement that a chromosome 3/17 rearrangement is associated with the retinoblastoma gene as claimed in claim 1 etc.

Claims 1-21, 26-28, 34, 39, 41, and 42 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 1-21, 26-28, 31, 34, 39, 41, 42, and 47 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to retinoblastoma rearrangement detection wherein there is used the specific primers showing chromosomal rearrangements involving chromosomes 13 and 21 as given in Example IX starting on page 130 of the specification. There is no guidance or enablement of involvement of other chromosomes or primers. There is especially no guidance as to what is meant as to the location of "the vicinity" given in claim 1, line 3. Additionally, the reference cited by applicants as Bowcock et al. has been enclosed in the previous office action and summarizes in the abstract that the linkage between the chromosome 13 RB gene and cancer is not clear and may be secondary or present in some tumors only be chance. Thus even the instantly discussed rearrangement is in question as to its enablement. See M.P.E.P. §§ 706.03(n) and 706.03(z).

Claims 1-21 and 29-34 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly

point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-21 and 29-33 are vague and indefinite in that they are supposedly method claims but do not recite even a single positive method step.

Claims 1-21, 31, and 34 are vague and indefinite in that they cite a nucleic acid sequence (e.g. claim 1, line 2) as if it was a composition. A "sequence" of a nucleic acid is a characteristic of said nucleic acid and not a composition in itself. Thus citing a sequence as a composition is confusing and unclear as to what is meant. Clarification is requested.

Claims 15-21 are rejected under 35 U.S.C. § 112, fourth paragraph, as being of improper dependent form for failing to further limit the subject matter of a previous claim.

Claims 15-21 broaden rather than further limit the scope of claim 1 from which each ultimately depends. Claim 1 is limited to probes only for chromosomes 3 and/or 17 and do not cover a scope including other chromosomes. Therefore, the added chromosomes 13 and 21 in claim 15 is not further limiting from claim 1.

35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claims 8-13, 28, and 33 are rejected under 35 U.S.C. § 101 because they are directed to a cancer detection utility,

prognosis, effectiveness of therapy, etc. that must be definite and in currently available form for which evidence is lacking in the instant disclosure. The data in Table 4 on page 135 is insufficient to show said utility clearly due to a lack of controls as well as data directed at diagnostic etc. determination that could be correlated between various samples. See the MPEP § 608.01(p), section on 35 U.S.C. 101.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 29, 30, 32, 33, and 46 are rejected under 35 U.S.C. § 102(e) as being clearly anticipated by Weissman et al.

Weissman et al. discloses in columns 5-6, bridging paragraph, that the invention therein described detects chromosomal arrangements such as the spacing between genes including linkage that may be related to a disease. Probed regions are disclosed as 50 kb to 2000 kb in column 9, lines 14-32, which clearly qualifies as high complexity probes as

instantly claimed. The coverage of the probed region is accomplished as depicted in Figure 5 (discussed in column 18, lines 32-62) and discussed as to probes prepared in the bridging paragraph between columns 18 and 19. This probe and hybridization practice clearly reads on the above rejected claims.

Claim 29 is rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Yunis et al.

The abstract of Yunis et al., the "Materials and Methods" technique, and the results shown in Figures 3-5 read on the rejected claims in that a method is disclosed where probes that will hybridize throughout the human gene complement show the localization of expressing genes and thus show staining of chromosomes that show differences due to expression between chromosomes as given in claim 29.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same

person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 1-21, 26-34, 39, 41, 42, 46, and 47 are rejected under 35 U.S.C. § 103 as being unpatentable over Weissman et al.

The instant invention is directed to high complexity probes and their use for hybridization labeling of chromosomes to detect rearrangements that may be associated with various disease states.

Weissman et al. discloses in columns 5-6, bridging paragraph, that the invention therein described detects chromosomal arrangements such as the spacing between genes including linkage that may be related to a disease. Probed regions are disclosed as 50 kb to 2000 kb in column 9, lines 14-32, which clearly qualifies as high complexity probes as instantly claimed. The coverage of the probed region is accomplished as depicted in Figure 5 (discussed in column 18, lines 32-62) and discussed as to probes prepared in the bridging paragraph between columns 18 and 19. Weissman et al. lacks the specific retinoblastoma rearrangement disclosure but is motivated to study such rearrangements as summarized in column 2, line 13, through column 4, line 5.

Thus, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to practice high complexity probes and their use in hybridization assay as instantly claimed because Weissman et al. discloses the method and the motivation to apply this to diseases suspected of being caused by genetic rearrangements such as retinoblastoma gene rearrangements that result in cancer.

The references cited herein have been made of record in the parent application 08/015,390 and are hereby also made of record in the instant application. Since copies have been previously sent to applicants, they are not herewith resent.

The disclosure is objected to because of the following informalities:

On page 18, the citation to Waldman et al. is incomplete.

On pages 131, 140, 144 and 145; lines 2, 11, 25, and 11; respectively; the citations are incomplete.

Appropriate correction is required.

No claim is allowed.

This is a File-Wrapper-Continuation of applicant's earlier application S.N. 08/015,390. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds or art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See M.P.E.P. § 706.07(b). Applicant is reminded of the extension of time policy as set

forth in 37 C.F.R. § 1.136(a). The practice of automatically extending the shortened statutory period an additional month upon the filing of a timely first response to a final rejèction has been discontinued by the Office. See 1021 TMOG 35.

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

The CM1 Fax Center number is (703) 305-3014 or (703) 308-4227.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ardin Marschel, Ph.D., whose telephone number is (703) 308-3894.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

AM

A. MARSCHEL:am
April 4, 1994

M. Parr 4/4/94

MARGARET PARR
SUPERVISORY PATENT EXAMINER
GROUP 1800

If applicant desires priority under 35 U.S.C. § 120 based upon a parent application, specific reference to the parent application must be made in the instant application. It is noted that this appears as the first sentence of the specification following the title. Status of the parent application (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "Patent No." should follow the filing date of the parent application. If a parent application has become abandoned, the expression "abandoned" should follow the filing date of the parent application.

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The title covers methods only whereas the instant claims are also directed to compositions. Also the title is lacking as to the retinoblastoma central aspect of the invention.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

On pages 137-147 of the specification there is described the detection of chromosome 3/17 aberrations. This is the only disclosure in the specification directed at these chromosomes. The cell lines studied are listed on page 141, first paragraph.

None of those cell lines nor the accompanying discussion involve the retinoblastoma gene as claimed in claim 1, for example. Thus there is a complete lack of instant enablement that a chromosome 3/17 rearrangement is associated with the retinoblastoma gene as claimed in claim 1 etc.

Claims 1-21, 26-28, 34, 39, 41, and 42 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 1-21, 26-28, 31, 34, 39, 41, 42, and 47 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to retinoblastoma rearrangement detection wherein there is used the specific primers showing chromosomal rearrangements involving chromosomes 13 and 21 as given in Example IX starting on page 130 of the specification. There is no guidance or enablement of involvement of other chromosomes or primers. There is especially no guidance as to what is meant as to the location of "the vicinity" given in claim 1, line 3. Additionally, the reference cited by applicants as Bowcock et al. has been enclosed in the previous office action and summarizes in the abstract that the linkage between the chromosome 13 RB gene and cancer is not clear and may be secondary or present in some tumors only be chance. Thus even the instantly discussed rearrangement is in question as to its enablement. See M.P.E.P. §§ 706.03(n) and 706.03(z).

Claims 1-21 and 29-34 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly

point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-21 and 29-33 are vague and indefinite in that they are supposedly method claims but do not recite even a single positive method step.

Claims 1-21, 31, and 34 are vague and indefinite in that they cite a nucleic acid sequence (e.g. claim 1, line 2) as if it was a composition. A "sequence" of a nucleic acid is a characteristic of said nucleic acid and not a composition in itself. Thus citing a sequence as a composition is confusing and unclear as to what is meant. Clarification is requested.

Claims 15-21 are rejected under 35 U.S.C. § 112, fourth paragraph, as being of improper dependent form for failing to further limit the subject matter of a previous claim.

Claims 15-21 broaden rather than further limit the scope of claim 1 from which each ultimately depends. Claim 1 is limited to probes only for chromosomes 3 and/or 17 and do not cover a scope including other chromosomes. Therefore, the added chromosomes 13 and 21 in claim 15 is not further limiting from claim 1.

35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claims 8-13, 28, and 33 are rejected under 35 U.S.C. § 101 because they are directed to a cancer detection utility,

prognosis, effectiveness of therapy, etc. that must be definite and in currently available form for which evidence is lacking in the instant disclosure. The data in Table 4 on page 135 is insufficient to show said utility clearly due to a lack of controls as well as data directed at diagnostic etc. determination that could be correlated between various samples. See the MPEP § 608.01(p), section on 35 U.S.C. 101.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 29, 30, 32, 33, and 46 are rejected under 35 U.S.C. § 102(e) as being clearly anticipated by Weissman et al.

Weissman et al. discloses in columns 5-6, bridging paragraph, that the invention therein described detects chromosomal arrangements such as the spacing between genes including linkage that may be related to a disease. Probed regions are disclosed as 50 kb to 2000 kb in column 9, lines 14-32, which clearly qualifies as high complexity probes as

instantly claimed. The coverage of the probed region is accomplished as depicted in Figure 5 (discussed in column 18, lines 32-62) and discussed as to probes prepared in the bridging paragraph between columns 18 and 19. This probe and hybridization practice clearly reads on the above rejected claims.

Claim 29 is rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Yunis et al.

The abstract of Yunis et al., the "Materials and Methods" technique, and the results shown in Figures 3-5 read on the rejected claims in that a method is disclosed where probes that will hybridize throughout the human gene complement show the localization of expressing genes and thus show staining of chromosomes that show differences due to expression between chromosomes as given in claim 29.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same

person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 1-21, 26-34, 39, 41, 42, 46, and 47 are rejected under 35 U.S.C. § 103 as being unpatentable over Weissman et al.

The instant invention is directed to high complexity probes and their use for hybridization labeling of chromosomes to detect rearrangements that may be associated with various disease states.

Weissman et al. discloses in columns 5-6, bridging paragraph, that the invention therein described detects chromosomal arrangements such as the spacing between genes including linkage that may be related to a disease. Probed regions are disclosed as 50 kb to 2000 kb in column 9, lines 14-32, which clearly qualifies as high complexity probes as instantly claimed. The coverage of the probed region is accomplished as depicted in Figure 5 (discussed in column 18, lines 32-62) and discussed as to probes prepared in the bridging paragraph between columns 18 and 19. Weissman et al. lacks the specific retinoblastoma rearrangement disclosure but is motivated to study such rearrangements as summarized in column 2, line 13, through column 4, line 5.

Thus, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to practice high complexity probes and their use in hybridization assay as instantly claimed because Weissman et al. discloses the method and the motivation to apply this to diseases suspected of being caused by genetic rearrangements such as retinoblastoma gene rearrangements that result in cancer.

The references cited herein have been made of record in the parent application 07/670,242 and are hereby also made of record in the instant application. Since copies have been previously sent to applicants, they are not herewith resent.

The disclosure is objected to because of the following informalities:

On page 18, the citation to Waldman et al. is incomplete.

On pages 131, 140, 144 and 145; lines 2, 11, 25, and 11; respectively; the citations are incomplete.

Appropriate correction is required.

No claim is allowed.

This is a File-Wrapper-Continuation of applicant's earlier application S.N. 07/670,242. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds or art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See M.P.E.P. § 706.07(b). Applicant is reminded of the extension of time policy as set

forth in 37 C.F.R. § 1.136(a). The practice of automatically extending the shortened statutory period an additional month upon the filing of a timely first response to a final rejection has been discontinued by the Office. See 1021 TMOG 35.

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Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

AM

A. MARSCHEL:am
April 19, 1993

Amelia B. Yarbrough
AMELIA BURGESS YARBROUGH
PRIMARY EXAMINER
ART UNIT ~~187~~ 1807